

Viral Hepatitis



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Focus

- Changes to Aeromedical Waiver Guide for Hepatitis in Aviators
- Aeromedical outcomes of aviators with hepatitis
-

Objectives

- Diagnose and manage hepatitis and its complications
- Examine the aeromedical outcomes of aviation personnel with hepatitis
- Be aware of policy changes in Aeromedical Waiver Guide

Past Waiver Guide Policy

- Revised August 1994
- Chronic Hepatitis B
- Chronic Hepatitis C

Chronic Hepatitis B Infection

- "... (either chronic persistent hepatitis or chronic active hepatitis) is disqualifying."
- "Waivers can be recommended for certain cases of chronic hepatitis B, provided liver biopsy shows no evidence of fibrosis, and hepatitis serology indicates some antibody formation."

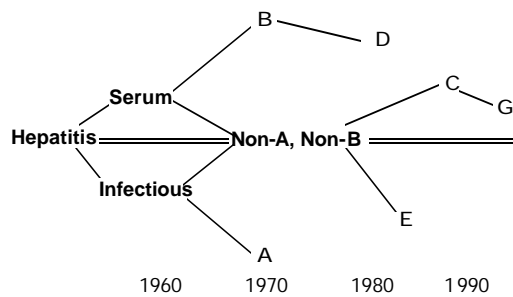
Chronic Hepatitis C Cases

- "...should be referred to NOMI for evaluation."

Current Management of Chronic HBV and HCV

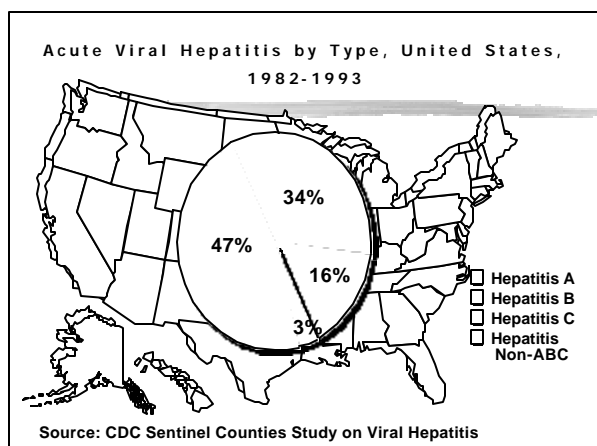
- Waivers recommended if following conditions are met:
- Asymptomatic
- Liver enzymes (AST, ALT) less than 2.5 times upper limit of normal
- No fibrosis on biopsy
- On no medications for chronic hepatitis

Historical Classification by Epidemiology



Complications

Type	Carrier	Cirrhosis	Cancer
A	No	No	No
E	No	No	No
B	5%	15-30%	Yes
C	70-85%	60%	Yes
D	Yes	70-80	?



Clinical Course of HBV

- Incubation- 40-180 days
 - Average 60-90 days
- Clinical illness (jaundice)
 - <5 yrs, <10%
 - 5 yrs, 30%-50%
- Many asymptomatic

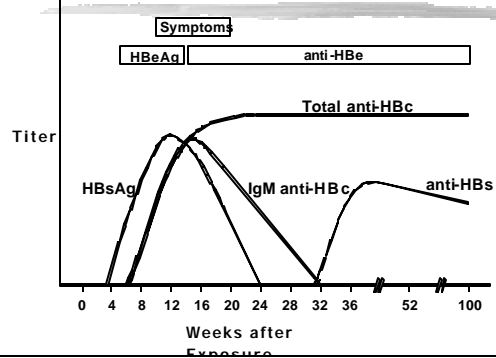
Clinical Course of HBV

- Fulminant- 1-3% of acute icteric cses
 - 90% mortality
- Acute case-fatality rate: 0.5%-1%

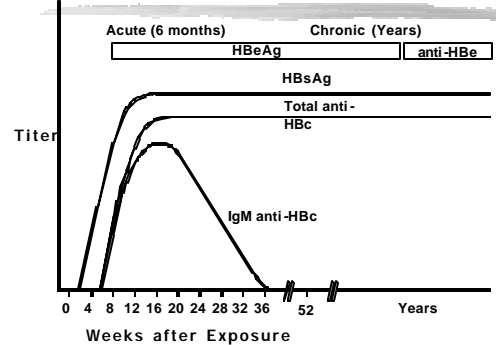
Clinical Course of HBV

- Self-limited in 95%
- Chronic infection:
 - <5 yrs, 30%-90%
 - 5 yrs, 2%-10%
- Premature mortality from chronic liver disease: 15%-25%

Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course



Diagnosis of Hepatitis B

Test	Significance	Infectious
HBsAg	Viral replication	Yes
Anti-HBcore	Infection- acute, chronic, resolved	Maybe
Anti-HBcore IgM	Recent infection	Maybe
Anti-HBs	Immunity	No
HBeAg	High viral replication	Highly
Anti-HBeAg	Decreased or no replication	Yes or No

HBV- Carrier State

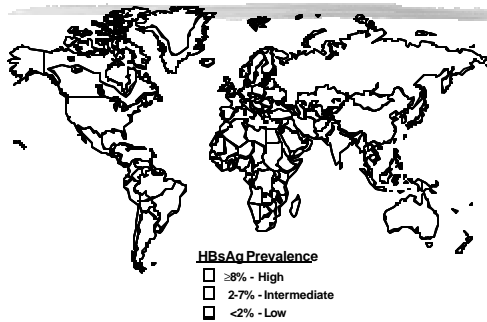
- 5% in adults
- 50% in children



Global Patterns of Chronic HBV Infection

- High (>8%): 45% of global population
 - lifetime risk of infection >60%
 - early childhood infections common
- Intermediate (2%-7%): 43% of global population
 - lifetime risk of infection 20%-60%
 - infections occur in all age groups
- Low (<2%): 12% of global population
 - lifetime risk of infection <20%
 - most infections occur in adult risk groups

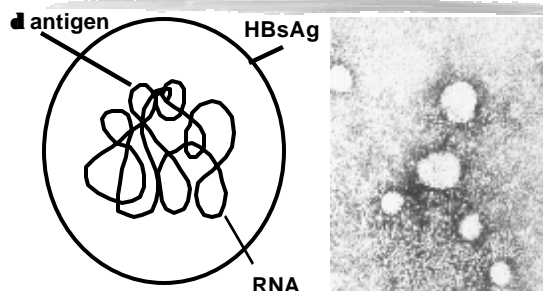
Geographic Distribution of Chronic HBV Infection



Hepatitis D (Delta Hepatitis)

- Incomplete RNA viral particle
 - Nucleoside antigen plus RNA
- Infects only in presence of HBsAg
- Uses HBsAg for its structural shell
- 1st detected by Rizetto in Italian chronic HBsAg carriers

Hepatitis D (Delta) Virus



HDV- Epidemiology

- Endemic in Mediterranean & Middle East
 - 20-40% of HBsAg carriers in Kuwait & Saudi Arabia
 - Rare in US, northern Europe, China
- Epidemics in isolated populations in developing world
 - South America, Amazon basin

HDV- Transmission

- IDU
- Blood products- hemophiliacs
- Sexual partners of IDU
- Intrafamilial

HDV- Clinical Course

- Acute or chronic
- More severe
- Case fatality rate- 2-20%
- Accelerated progression of chronic HBV
 - HDV- 70-80% develop cirrhosis
 - HBV alone- 15-30% develop cirrhosis

HDV- Forms

■ Co-infection

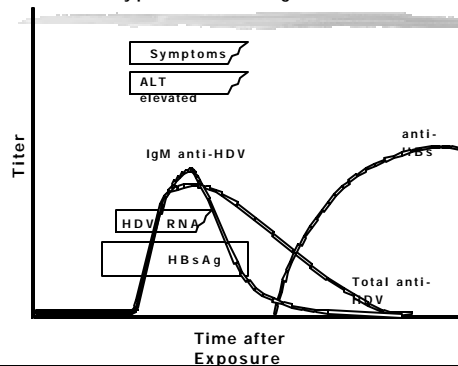
- Simultaneous occurrence of acute HDV & HBV
- Severe acute disease
- <5% develop chronic infection

■ Super-infection

- Appearance of acute HDV in chronic HBV
- HBsAg allows persistence of HDV
- >80% develop chronic hepatitis
- High risk of severe chronic liver disease

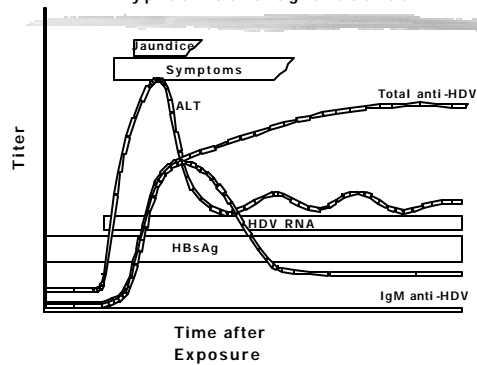
HBV - HDV Coinfection

Typical Serologic Course



HBV - HDV Superinfection

Typical Serologic Course



HDV- Diagnosis

■ Anti-HDV

- Delayed, short-lived, low titer in acute HDV
- Persists in low titer in chronic HDV

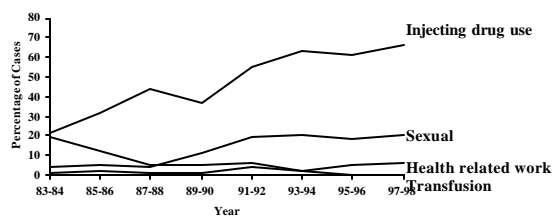
■ Research tests

- HDV antigen in serum and liver with immunoblotting
- HDV RNA by molecular hybridization

HCV- Transmission

- Parenteral exposure
- Sexual contact
- Vertical (perinatal) transmission

Reported Cases of Acute Hepatitis C by Selected Risk Factors, United States, 1983-1998*

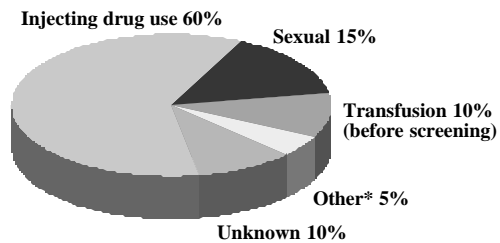


* 1983-1990 based on non-A, non-B hepatitis

Source: CDC Sentinel Counties Study



Sources of Infection for Persons with Hepatitis C

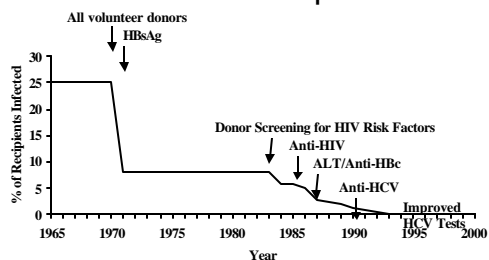


*Nosocomial; Health-care work; Perinatal

Source: Centers for Disease Control and Prevention



Posttransfusion Hepatitis C



Adapted from HJ Alter and Tobler and Busch, Clin Chem 1997



HCV- Sexual Contact

- Very low rate in contrast to HBV and HIV
- Married couples in Japan- discordant HCV status
 - No HCV RNA after 10 years of marriage
 - 9% with HCV RNA after 10-30 years of marriage
- Higher level of HCV infection in homosexuals

HCV Prevalence in US Populations

Characteristic	HCV Prevalence (%)	Proportion of Population (%)
Hemophilia	87	<0.01
STD	5	17
Blood Transfusion Before 1990	5	6
General Population	1.8	
Military	0.2	0.5
Blood Donors	0.16	5

CDC. MMWR 1998;47(RR-19)

HCV- Chronic Hepatitis

- 70-85% of infected persons
- Independent of mode of acquisition
- Symptoms not predictive of severity or cirrhosis
- Physical signs absent
- Erratic fluctuations of transaminases
 - Emergence of mutant quasispecies
- HCV- cause of 50% of chronic hepatitis in US

Chronic HCV- Natural History

- Spontaneous HCV loss- rare (0.6/100 patient years)
- Indolent course- 20 or more years to cirrhosis
- Progression in 60%
- Cirrhosis in 20-25%
- Independent risk factor for hepatocellular carcinoma

Diagnosis of Hepatitis C

Test	Application
EIA	Screening
RIBA	Confirmation
HCV-RNA Qualitative	Confirmation Response to RX
HCV-RNA Quantitative	Likelihood of response to RX

HCV Antibody Tests

- EIA- Screening test
 - 97% sensitivity
 - Past or present infection
 - Low PPV in low prevalence population
- RIBA- Confirmatory test

HCV RNA Tests

- Qualitative (RT-PCR)
 - Approved by FDA
 - Detects virus 1-2 weeks after infection
 - Negative test does not exclude infection
 - Indication for treatment
 - Disappearance indicative of response to RX
- Quantitative (RT-PCR or bDNA)
 - Lack of standardization
 - Less sensitive than qualitative

Treatment of Chronic Hepatitis

- HBV
- HCV

HCV- Indications for Treatment

- Chronic HCV
- Persistently elevated ALT/AST
- Positive HCV RNA
- Liver biopsy
 - Portal or bridging fibrosis
 - Moderate degrees of inflammation or necrosis

HCV- Treatment

- Immunomodulatory therapy
 - Interferon alfa -2b recombinant (Inton A)
 - Pegylated interferon
- Antiviral therapy
 - Ribavirin (Rebetol) capsules
 - Approved in 1998

HCV- Interferon alfa

- 3 million units 3 times /week for 6 months
- Biochemical response- 50%
- Relapse- 70% in 6-12 months
- Predictors of poor response
 - High serum HCV RNA
 - Advanced histologic disease
 - Possibly HCV genotype

HCV- Combination Therapy

- Ribavirin + interferon alfa
- Not a cure
- Suppresses blood levels of HCV better than IF-*a* alone

HCV- Combination Therapy

- Reduced HCV levels at 6 months
 - Combination- 45%
 - IF-*a* alone- 5%
- Reduced inflammation
 - Combination- 50%
 - IF-*a* alone- 34%

Pegylated IF-a

- Recombinant IFa-2b conjugated to polyethylene glycol
- PEG-Intron (Schering) approved by FDA
 - 1 ug/kg SC weekly for 48 weeks
- Pegylation delays IF clearance
- Peak serum concentrations higher
- Troughs are minimized

HCV- Combination Therapy- Adverse Effects

- Headache, fatigue, myalgia, fever
- Psychiatric disorders
 - Depression, suicidal behavior
- Anemia- Ribavirin

Treatment of Chronic HBV

- Immunomodulatory therapy
 - Interferon alfa
- Antiviral therapy
 - Lamivudine (3TC, Epivir)
 - Reverse transcriptase inhibitor

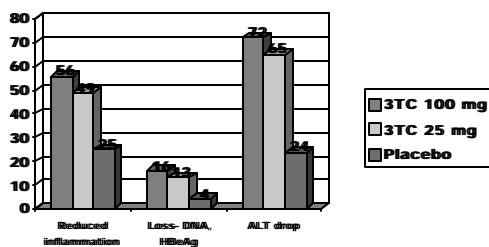
HBV- Interferon alfa

- 30-40% response rate
 - Loss of HBV e antigen
 - Loss of HBV DNA from serum
- Most responders remain in remission for years
- Flare of disease with treatment initiation
- Dose- 5 million units daily SC or 10 million units SC 3 times a week for 16 weeks

HBV- Lamivudine

- Antiretroviral reverse transcriptase inhibitor
- HBV polymerase has reverse transcriptase activity
- Conclusions- safe, effective
 - Resistance may limit usefulness

HBV- 1 Year Trial of Lamivudine



Other Issues

- Effect of viral hepatitis on Walking Blood Bank
- Routine screening of military or aviation personnel for HCV

8201. WALKING BLOOD BANK (WBB)

- Volunteer donors only
- Free of disease transmissible by blood transfusion (viral hepatitis, malaria, syphilis, HIV, etc.).
- DD Form 572 will be completed and updated annually by each member
- COMNAVAIRPACINST 6000.2C/
COMNAVAIRLANTINST 6000.1E

Screening for HCV

- Seroprevalence in US military- 0.2%
- Low positive predictive value of HCV EIA in low prevalence population
- Cost of initial screening EIA
- Cost of confirmatory RIBA in false positive EIA

Methods

- Search of NAMI Biomedical Database (Access)
- Review of records (1 record missing)
 - Microfiche
 - NAMI Reviewer
 - Workflow - Eastman Software Document Management Station

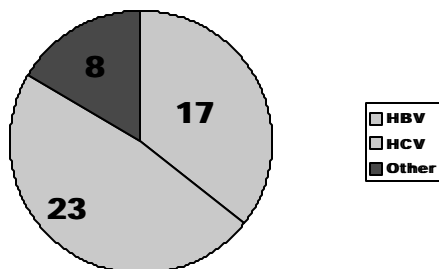
Results- Waiver Requests

- 48 naval aviation personnel from July 1988 to May 2001
- 42 men and 6 women
- 95 follow-up PE's
- Total of waiver requests or renewals- 143

Class of PE

<i>Class</i>	<i>Count</i>	<i>Percent</i>
<i>Pilot</i>	10	20.8
<i>NFO</i>	10	20.8
<i>Aircrew</i>	20	41.7
<i>ATC</i>	7	14.6
<i>Aeromedical</i>	1	2.1
<i>Total</i>	48	100

Type of Hepatitis



Other Types of Hepatitis

- Autoimmune hepatitis (AIH)- 2
- Alcoholic- 2
- Non A, non B (NANBH)- 1
- Steatohepatitis- 1
- Unknown- 2
 - Hodgkin's lymphoma and CPH on biopsy
 - Acquired hemolytic anemia, idiopathic myocarditis, ITP, acute renal failure

Indications for Viral Serology

Indication	B	C	Total
Blood donor	8	7	15
Family contact	1		1
Prior history	1		1
Symptomatic	1		1
Occupational PE		3	3
Other		4	4

Other Indications for Viral Serology

- Chemical hepatitis on INH chemoprphylaxis- 1
- Dermatology evaluation- 1
- Neurology evaluation- 1
- STD screening after contact in West PAC- 1

Type of Hepatitis and Race

Hepatitis	Caucasian (%)	Black (%)	Asian (%)
HBV	10 (58.8)	1 (5.9)	6 (35.3)
HCV	22 (95.7)		1 (4.3)
Total	38 (82.6)	1 (2.2)	7 (15.2)

Waiver Status

Hepatitis	Recommended (%)	Waiver Previously Granted (%)	Not Recommended (%)
B	12 (70.6)	1 (5.9)	4 (23.5)
C	16 (69.6)	1 (4.4)	6 (26.1)
Other	2 (25)		6 (75)
Total	30 (62.5)	2 (4.2)	16 (33.3)

Follow-up on Waiver Recipients

- 32 initial waiver recipients
- 1 subsequent waiver for HCV after IF-a therapy
- 1 subsequent waiver after Hodgkin's lymphoma in remission
- Total of 34 (70.8 %) waivers

Waivers Later Revoked

- 2 waivers revoked
- Symptomatic- 1
- Incomplete PE- 1

USAF Aeromedical Consult Service

- 1985-2000- 25 total cases of hepatitis
- Seven referred with hepatitis as the primary diagnosis
 - Chronic persistent hepatitis- 5 (one with possible Gilbert's syndrome)
 - Chronic active hepatitis- 1
 - Niacin induced hepatitis- 1
- Waivers for 5 with CPH

Conclusions

- Aviation personnel who receive waivers for asymptomatic viral hepatitis usually do not suffer relapse requiring revocation of waiver

Changes to Waiver Guide

- Chronic HBV
- Chronic coinfection or superinfection with HDV and HBV
- Chronic HCV

Chronic Hepatitis B

- Waivers are not considered for applicants.
- Waivers can be recommended for designated members with chronic hepatitis B, provided liver enzymes are less than 100 U/L or 2.5 times upper limits of normal, liver biopsy shows only mild inflammation and no evidence of fibrosis, and member is asymptomatic.

Chronic HDV and HBV

- Chronic coinfection or superinfection with HDV and HBV is disqualifying without waiver considered because of the more frequent and severe symptomatology and greater risk of progression.

Chronic HCV

- Waivers are not considered for applicants.
- Waivers can be recommended for designated members with chronic hepatitis C, provided liver enzymes are less than 100 U/L or 2.5 times upper limits of normal, liver biopsy shows only mild inflammation and no evidence of fibrosis, qualitative HCV PCR is negative, and member is asymptomatic.

Questions
